UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/907,041	08/06/1997	JOEL S. GREENBERGER	76333.103	7766

7590 04/24/2002

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 200075109

EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	26

DATE MAILED: 04/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/907,041	Applicant(s) GREENBERGER, JOEL S.
	Examiner Shin-Lin Chen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-20-02 has been entered.

Applicant's reply accompanied with Request for Continued Examination filed 3-20-02 has been entered. Claims 1-31 are pending and under consideration.

Priority

1. It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 08/136,079, filed 10-15-93. A reference to the prior application must be inserted as the first sentence of the specification of this application if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 5,599,712(A). Although the conflicting claims are not identical, they are not patentably distinct from each other because although drawn to different scope, they encompass the same invention and obvious variants thereof.

The claimed invention of the present application is drawn to a method for protecting a subject against an agent that elicits free radicals, superoxide anions, or heavy metal cations, said method comprising the steps of administering to said subject a pharmaceutical composition comprising a polynucleotide that encodes a protein transiently expressed in said subject, and said pharmaceutical composition. The claims of '712 are drawn to a method for protecting a **cancer** subject against an agent that elicits free radicals, superoxide anions, or heavy metal cations, said method comprising the steps of administering **directly to the site of the tumor** in said subject a pharmaceutical composition comprising a polynucleotide that encodes **a gamma glutamyl transpeptidase, a manganese superoxide dismutase, or a metallothionein**, transiently expressed in said subject, and said pharmaceutical composition. The claims of the present

application clearly encompass the claims of '712. Claims 17 and 18 specify the polynucleotide is under the control of an inducible or radioinducible transcriptional regulatory sequence, and claim 30 specifies the polynucleotide is stably integrated into the genome of the subject. Since the polynucleotide is intended to be expressed in the subject, it would have been obvious for one of ordinary skill at the time of the invention to use a regulatory sequence either inducible or not inducible to activate the expression of the polynucleotide in the subject, and the use of inducible or not inducible regulatory sequence depends on the intended targeted tissue(s) or organ(s) of the subject. Further, the integration of the polynucleotide into the genome of the cell of a subject also would have been obvious for one of ordinary skill at the time of the invention because whether the polynucleotide would integrate into the genome of a cell depends on the type of the vector and the component within said vector used. Thus, claims 1-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 5,599,712(A).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for radiation-resistant of murine melanoma cell line B16 via higher expression of γ-GTP, expression of a MnSOD transgene under control of the irradiation inducible egr-1 promoter that increases the radioresistance of 32D CL 3 hematopoietic progenitor cells *in vitro*, and protection of cells from irradiation via administration of polynucleotide encoding MnSOD, MT, or gamma-GTP to a subject locally to the targeted site, does not reasonably provide enablement for a method for protecting any subject against an agent that produces toxic species including free radicals, superoxide anions, and heavy metals, by administering a pharmaceutical composition, comprising a polynucleotide or any vector encoding a protein that is capable of neutralizing or eliminating said toxic species, to said subject **via systemic administration routes** to protect any targeted site *in vivo*, and said pharmaceutical composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-31 are directed to a method for protecting a subject against an agent that elicits free radicals, superoxide anions, or heavy metal cations, said method comprising the steps of administering to said subject *in vivo* a pharmaceutical composition comprising a polynucleotide that encodes a protein transiently expressed in said subject, and a pharmaceutically acceptable vehicle for said polynucleotide; and a pharmaceutical composition comprising said polynucleotide in a pharmaceutically acceptable vehicle.

The specification discloses the construction of recombinant adenoviral vectors Ad-MT, Ad-MnSOD, and Ad-γ-GTP; the expression of metallothionein (MT), manganese superoxide dismutase (MnSOD), and γ-Glutamyltranspeptidase (γ-GTP) in rat lung epithelium *in vivo*, and the function assay for MT, MnSOD, and γ-GTP proteins. The specification discloses expression of greater levels of γ-GTP in murine melanoma cell line B16 renders the cell line less sensitive to γ-irradiation, and expression of a MnSOD transgene under control of the irradiation inducible egr-1 promoter increases the radioresistance of 32D CL 3 hematopoietic progenitor cells *in vitro*.

The claims encompass protecting a subject from an agent producing toxic species by administering a pharmaceutical composition comprising a polynucleotide encoding a protein that is able to neutralize said toxic species via **any administration routes** *in vivo*. The post-filing evidence provided in the reply submitted 3-20-02 only discloses protection of cells from radiation via local administration of a polynucleotide encoding MnSOD, such as intratracheal injection, intraesophageal injection, or direct injection into small intestine. The specification fails to provide adequate guidance and evidence that systemic administration of a polynucleotide encoding a protein capable of neutralizing toxic species can protect any targeted site in a subject *in vivo*. The specification also fails to provide adequate guidance and evidence that administration of a polynucleotide encoding a protein capable of neutralizing toxic species to a site that is very remote from the site to be treated with irradiation can protect cells in any targeted site in a subject *in vivo*.

The phrase "pharmaceutical composition" in claims 27-29 implies therapeutic effect *in vivo*. Thus, claims 1-31 read on gene therapy *in vivo*. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell

population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA are all important factors for a successful gene therapy (e.g. bridging pages 81-82). It is unclear whether administration of a polynucleotide or any vector encoding a protein capable of neutralizing toxic species via any systemic administration route or via administration of said polynucleotide or vector to a site that is very remote from the site to be treated with irradiation can still protect cells in any targeted site in a subject *in vivo*. One skilled in the art would not know how to use the claimed pharmaceutical composition to practice over the full scope of the invention claimed.

For the reasons discussed above, it would require undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 27 and 28 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Morrow, 1994 (US Patent No. 5,334,383).

Claims 27 and 28 are directed to a pharmaceutical composition comprising a polynucleotide that encodes a protein that is capable of neutralizing or eliminating toxic species, such as a free radical, a superoxide anion, or a heavy metal, and a pharmaceutically acceptable vehicle for said polynucleotide. Claim 28 specifies the polynucleotide encodes a gamma glutamyl transpeptidase (gamma-GTP), a manganese superoxide dismutase (Mn-SOD), or a metallothionein (MT).

Morrow teaches administration of moderating and/or neutralizing amounts of antioxidants or reducing agents, such as catalase, superoxide dismutase or glutathione perxoidase etc., along with an electrolyzed saline solution to a subject, wherein said antioxidants or reducing agents remove the superoxides, peroxides and hydroxides produced by respiratory bursts in the cells. The superoxide dismutase (SOD) includes Cu, Zn-superoxide, Mn-SOD and Fe-SOD (e.g. column 3, 5). The buffer solution containing the antioxidants and/or reducing agents is considered a pharmaceutically acceptable vehicle. Thus, claims 27 and 28 are clearly anticipated by Morrow.

It should be noted that the term "pharmaceutical" does not carry weight in 102(e) rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

Chen